Appl. No. 09/586,529
Amdt. dated January 12, 2004
Reply to Office Action of September 12, 2003

PATENT

## REMARKS/ARGUMENTS

### I.    *Status of the Claims*

Claims 26 and 27 are added.  Claims 1-6 and 10-27 are pending with entry of this Amendment.

### II.    *Support for the Amendments*

Support for the amendments to the claims can be found throughout the specification, the drawings, and the claims as originally drafted.  Support for new claim 26 can be found on, e.g., page 28, lines 22-23 and page 27, lines 20-24 of the specification.  Support for new claim 27 can be found on, e.g., page 7, line 5 of the specification.  No new matter is introduced with this amendment.

### III.    *Rejections under 35 U.S.C. § 103*

The Examiner rejected all of the pending claims as allegedly obvious over Brosch *et al.* or Kelley *et al.* or Roach *et al.* in view of Knight *et al.* or Mitelman *et al.* or Kleinjan *et al.* or Eppig *et al.* in further view of Altshul *et al.*  Applicants respectfully traverse each of these rejections.

The Examiner has not set forth a *prima face* obviousness rejection.  As discussed in detail below, the rejections at a minimum fail to teach or suggest the following steps in claim 1:

(iii) identifying a pair of sequences within said reference genome that corresponds to each of said pairs of terminal sequences; and

(iv) determining the relationship between the members of each pair of corresponding sequences within said reference genome

As a general matter, none of the primary references teach using end sequencing for any purpose other than to align BAC or other clones.  None of the primary references but Brosch *et al.* even mention comparing two genomes, and Brosch *et al.* does <u>not</u> teach or suggest identifying pairs of sequences in a reference genome that correspond to the pairs of terminal

sequences in a clone from the test genome. None of the secondary references cited by the Examiner correct this problem. Accordingly, the rejection should be withdrawn.

Moreover, Applicants note that new claim 26 is further patentable in that the claim involves comparisons of sequence information by a computer. While Applicants acknowledge that the Examiner has cited Alschul *et al.*, which teaches BLAST computer sequence alignments, the Examiner has not pointed to any motivation in the art for comparing end sequences of clones with sequences from another sequenced genome to identify corresponding sequences or determining the relationship between the corresponding sequences. Generally, the Examiner has identified references that rely on hybridization, not nucleotide sequence information, to examine DNA. Accordingly, new claim 26 is also patentable over the cited art.

Furthermore, claim 27 is directed to embodiments employing cDNA clones according to the method of claim 1. All of the references cited by the Examiner are directed to end-sequencing genomic clones to identify overlapping clones to form a "contig" for genomic cloning purposes. There is no motivation in the cited art to end sequence cDNA clones, which are not contiguous, let alone to identify their corresponding sequences in another genome and then determine the relationship of the various end sequences in the genomes. Accordingly, new claim 27 is also patentable over the cited art.

### Brosch et al.

The Examiner states that "[s]equences of termini of the clones is determined and used for either establishing BAC map of the parent genome, or for comparative genomic studies of other genomes." This statement is not correct. There is absolutely no reference in Brosch *et al.* regarding **use of end sequences for comparative genomic studies**.

Indeed, in the last response, Applicants stated the same point:

> The paragraph specifically cited by the Examiner
> describes a method of digesting genomic clones and
> probing the restricted clones with labeled total DNA
> from another bacterial species. *See, e.g.,* third
> sentence of the second paragraph of page 2228 of
> Brosch *et al.* This method appears to be the only

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> method of genomic comparison described in any way in
> the reference. This method does not involve
> sequencing termini of clones, identifying
> corresponding sequences in a reference genome or
> determining the relationship between the members of
> each pair of termini as recited in the claims.

*See*, Response filed April 17, 2003, page 5.

Even if the terminal sequence information of clones is used for detection of differences with *M. bovis* as the Examiner suggests (top of page 3 of Office Action), the reference does not teach "**identifying a pair of sequences within said reference genome** that corresponds to each of said pairs of terminal sequences," as recited in claim 1. A review of page 2226 of Brosch *et al.* reveals that they cleave each BAC clone with a restriction enzyme, blot it and probe it with another genome. Brosch *et al.* does not identify sequences in the *M. bovis* genome that correspond to the **end** sequences of the BAC clones they identify from the *M. tuberculosis* genome. Indeed, review of the results illustrated in Figure 4 of Brosch *et al.* indicates that it is impossible to tell which band of the BAC clones represents the ends of the clones. Thus, Brosch *et al.* does not teach or suggest identifying a pair of sequences within the reference genome that corresponds to each of said pairs of terminal sequences; or determining the relationship between the members of each pair of corresponding sequences within the reference genome as recited in steps iii and iv of claim 1.

None of the secondary references cited by the Examiner (Knight *et al.* or Mitelman *et al.* or Kleinjan *et al.*, Eppig *et al.* or Altshul *et al.*) corrects the defects described above. The first four secondary references appear to only be cited for the proposition that those of skill in the art understood that chromosomal rearrangements could lead to disease. The last secondary reference cited appears to be cited for the proposition that DNA sequences can be compared. None of the above-listed references however teach or suggest identifying sequences in a reference genome corresponding to end sequences of clones from a test genome or determining the relationship between the members of each pair of corresponding sequences within the reference genome. Accordingly, the obviousness rejection fails.

Appl. No. 09/586,529
Amdt. dated January 12, 2004
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### Roach *et al.*

The Examiner also cited Roach *et al.*, in combination with the above-discussed secondary references, as rendering the present claims obvious. According to the Examiner, Roach *et al.* states that use of pairwise strategies is beneficial for fine scale mapping, gene finding and low- and high-pass sequencing. The Examiner appears to assert that the reference includes all of the limitations of the present claims except for use of end sequence profiling for genome analysis of individuals with a diseases associated with chromosomal rearrangements. Applicants respectfully traverse the rejection.

The Roach *et al.* reference is only directed to optimizing "pairwise end sequencing," to align (i.e., "contig") clones from a genome. While Roach *et al.* may describe obtaining end sequences from clones, the reference **does not teach or suggest** the following steps of claim 1:

> (iii) identifying a pair of sequences within said reference genome that corresponds to each of said pairs of terminal sequences; and
>
> (iv) determining the relationship between the members of each pair of corresponding sequences within said reference genome,

nor does the reference, as the Examiner admits, teach use of genome comparison to analyze disease. Indeed, Applicants note that the Office Action itself does not explain how or where Roach *et al.* discusses steps iii or iv of claim 1.

As discussed above, the secondary references cited by the Examiner do not correct the defects of the primary reference for the same reasons discussed above. Accordingly, the cited references do not render the claims obvious and Applicants request withdrawal of the rejections.

### Kelley *et al.*

The Examiner also cited Kelley *et al.*, in combination with the above-discussed secondary references, as rendering the present claims obvious. The Examiner appears to assert that the reference includes all of the limitations of the present claims except for use of end

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sequence profiling for genome analysis of individuals with a diseases associated with chromosomal rearrangements. Applicants respectfully traverse the rejection.

Like Roach *et al.* described above, Kelley *et al.* **does not teach or suggest** the following steps of claim 1:

> (iii) identifying a pair of sequences within said reference genome that corresponds to each of said pairs of terminal sequences; and
>
> (iv) determining the relationship between the members of each pair of corresponding sequences within said reference genome,

nor does the reference, as the Examiner admits, teach use of genome comparison to analyze disease.

Also like rejection based on Roach *et al.*, Applicants note that the Office Action itself does not explain how or where Kelley *et al.* discusses these steps of claim 1. At most, the Office Action on page 3 states that "[t]he reference states that BAC library and the end sequence dataset are representative of the genome (p. 1545, right column)." Applicants believe that the Examiner intended to refer to page 1545, **left** column. In any case, it appears that the "representation of the genome," taken in context, was intended to indicate that the BAC contig described in the reference included all of the DNA in the human genome. It is not clear how the fact that the BAC library and end sequence dataset representing the genome teaches or suggests identifying a pair of sequences within a reference genome corresponding to the end sequences and then determining the relationship between the members of each pair of corresponding sequences in the reference genome. Accordingly, Applicants respectfully request withdrawal of the rejection.

As discussed above, the secondary references cited by the Examiner do not correct the defects of the primary reference for the same reasons discussed above. Accordingly, the cited references do not render the claims obvious and Applicants request withdrawal of the rejections.

### Further Evidence of Non-Obviousness

Assuming *arguendo* a *prima facie* case of obviousness has been made, objective indicia of non-obviousness successfully rebuts the *prima facie* showing. *See, Rosemount, Inc., v. Beckman Instruments, Inc.*, 221 USPQ 1 (Fed. Cir. 1984); *Dow Chemical co. v. American Cyanamid Co.*, 2 USPQ2d 1350 (Fed. Cir. 1987). Objective evidence of non-obviousness includes commercial success, fulfillment of a long-felt need and unexpected results,. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986).

As that the present invention is not obvious, Applicants provide herein evidence that Applicants received a significant grant (approximately $1.7 million) under the National Cancer Institute Innovative Molecular Analysis Technologies (IMAT) program for the present invention. This program, as the name indicates, is directed to <u>innovative</u> technologies for molecular analyses. Applicants have provided herein printouts from the National Cancer Institute website describing the IMAT program and a page indicating that the present invention has received an IMAT award. For the Examiner's convenience, the actual webpages are printed out. In addition, the text of the webpages was pasted into a word processing application and re-printed so that the entire text can be read. Finally, Applicants have included a copy of a "Summary Statement" for the grant indicating the amount of the award.

Applicants submit that this award is strong evidence that those of skill in the art (i.e., the peer reviewers of the grant) believed that the invention was innovative (i.e., non-obvious). Indeed, the size of the grant is evidence that those of skill in the art consider the present invention particularly exciting, important and innovative. Accordingly, Applicants respectfully request withdrawal of the rejection.
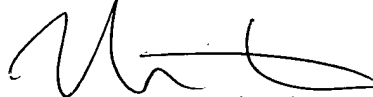
## CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this

Application are in condition for allowance. The issuance of a formal Notice of Allowance at an

early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of

this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

Matthew E. Hinsch
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❖ **unconventional innovations program**

❖ **fundamental technologies for biomolecular sensors**

❖ **development and testing of digital mammography displays and workstations**

❖ **development of clinical imaging drugs and enhancers**

❖ **early detection research network**

❖ **in vivo cellular**

**Collins, Colin**
University of California San Francisco

*Development of ESP: Structural & Functional Oncogenomics*

DESCRIPTION (Applicant's Description): The long-term objective of this proposal is to ga enhanced understanding of the structural genomics of solid tumors through development sequence-based method capable of identifying all types of structural rearrangements that tumor genomes. Genome rearrangements can promote cancer development, progression resistance to therapy by altering gene regulation and/or function, and the involved genes therapeutic targets. This is well established in leukemia and lymphoma, but less so in soli part because of the difficulty of identifying the genes involved in complex structural rearra describe here a powerful and high resolution, sequence-based analytical approach called Sequence Profiling (ESP). ESP maps copy number aberrations and directly identifies anc masse genome breakpoints associated with genome rearrangements such as inversions, translocations, deletions and amplifications. ESP is accomplished by constructing a BAC tumor genome, end sequencing a larger number of BAC clones, and mapping the BAC ei (BES) onto the normal genome sequence. Paired BES that map to different parts of the n span structural rearrangements. Sequencing these clones will reveal exact breakpoints a genes. In Specific Aim 1 we will: Implement ESP as a cost effective sequence-based tech determining the structural organization of tumor genomes and clone rearrangement breal masse. Determine the minimum sequencing depth needed to yield the maximum structur; Determine if ESP can reproducibly identify recurrent rearrangements between tumors, an whether specific sequence elements are associated with these rearrangements. In Specif will: Develop robust computational methods for the analysis, visual representation, and in ESP data with the human reference sequence, making possible comparison of ESP data independent tumors. Knowledge of how genome rearrangements such as inversions and impact local gene expression is critical. Thus, we will integrate ESP-based structure data expression microarray data and co-localize aberrantly expressed genes with genome rea breakpoints. In Specific Aim 3: We will biologically and clinically validate key ESP finding; ESP provides a rational framework for sequencing tumor genomes. In fact, 100 tumor gei analyzed at 10 kb resolution for less than sequencing a single 3000 Mb genome yielding novel biomarkers and therapeutic targets associated with translocations, inversions, and rearrangements. This is important because, just as a comprehensive systems-based kno\ human biology is predicated on the structural organization and sequence of the human g« structure-based view of tumor genomes is essential for a comprehensive understanding c biology.

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**Collins, Colin**
University of California San Francisco

***Development of ESP: Structural & Functional Oncogenomics***

DESCRIPTION (Applicant's Description): The long-term objective of this proposal is to gain an enhanced understanding of the structural genomics of solid tumors through development of a novel, sequence-based method capable of identifying all types of structural rearrangements that occur in tumor genomes. Genome rearrangements can promote cancer development, progression and/or resistance to therapy by altering gene regulation and/or function, and the involved genes are potential therapeutic targets. This is well established in leukemia and lymphoma, but less so in solid tumors, in part because of the difficulty of identifying the genes involved in complex structural rearrangements. We describe here a powerful and high resolution, sequence-based analytical approach called End Sequence Profiling (ESP). ESP maps copy number aberrations and directly identifies and clones en masse genome breakpoints associated with genome rearrangements such as inversions, translocations, deletions and amplifications. ESP is accomplished by constructing a BAC library of a tumor genome, end sequencing a larger number of BAC clones, and mapping the BAC end sequences (BES) onto the normal genome sequence. Paired BES that map to different parts of the normal genome span structural rearrangements. Sequencing these clones will reveal exact breakpoints and involved genes. In Specific Aim 1 we will: Implement ESP as a cost effective sequence-based technology for determining the structural organization of tumor genomes and clone rearrangement breakpoints en masse. Determine the minimum sequencing depth needed to yield the maximum structural information. Determine if ESP can reproducibly identify recurrent rearrangements between tumors, and if so, whether specific sequence elements are associated with these rearrangements. In Specific Aim 2 we will: Develop robust computational methods for the analysis, visual representation, and integration of ESP data with the human reference sequence, making possible comparison of ESP data from independent tumors. Knowledge of how genome rearrangements such as inversions and translocations impact local gene expression is critical. Thus, we will integrate ESP-based structure data with expression microarray data and co-localize aberrantly expressed genes with genome rearrangement breakpoints. In Specific Aim 3: We will biologically and clinically validate key ESP findings. We believe ESP provides a rational framework for sequencing tumor genomes. In fact, 100 tumor genomes can be analyzed at 10 kb resolution for less than sequencing a single 3000 Mb genome yielding hundreds of novel biomarkers and therapeutic targets associated with translocations, inversions, and complex rearrangements. This is important because, just as a comprehensive systems-based knowledge of human biology is predicated on the structural organization and sequence of the human genome, a structure-based view of tumor genomes is essential for a comprehensive understanding of tumor biology.

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# Innovative Molecular Analysis Technologies

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  ∟ **publications**
  ∟ **investigators meetings**
  ∟ **resources**

❖ **unconventional innovations program**

❖ **fundamental technologies for biomolecular sensors**

❖ **biology-chemistry centers**

❖ **development and testing of digital mammography displays and workstations**

❖ **development of clinical imaging drugs and enhancers**

Since the 1970s, it has become clear that cancer is not one disease, but many, and that c from the gradual accumulation of genetic changes in single cells. Identifying the molecula that distinguish any particular cancer cell from a normal cell ultimately helps define the na predict the pathologic behavior of that cancer cell, as well as its responsiveness to treatm

Knowledge of molecular alterations also assists in the identification of new targets and ap more effective interventions. Understanding the profile of molecular changes in a cancer i possible to correlate the resulting phenotype of that cancer with molecular events and us correlations to develop more effective strategies of detection, diagnosis, treatment, and p

Realizing this goal will require the National Cancer Institute (NCI) to develop and apply ne technologies that enable the identification of molecular changes that distinguish cancers f cells. New technologies will be needed to analyze the genes and gene products in isolate vitro, in living cells, and in whole animals and the living body.

The Innovative Molecular Analysis Technologies (IMAT) Program supports research proje and carry out pilot applications of novel technologies that will enable the molecular analys and their host environment in support of basic, clinical, and epidemiological research.

Technologies supported through the IMAT program include those that:

- detect alterations and instabilities of genomic DNA
- measure the expression of genes and gene products
- analyze and detect gene and/or cellular products including post-translational modi function of proteins
- identify and characterize exogenous infectious agents in cancer
- assay the function of major signal transduction networks involved in cancer

The program does not support resources such as databases and tissue repositories.

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# Innovative Molecular Analysis Technologies

Since the 1970s, it has become clear that cancer is not one disease, but many, and that cancers arise from the gradual accumulation of genetic changes in single cells. Identifying the molecular alterations that distinguish any particular cancer cell from a normal cell ultimately helps define the nature and predict the pathologic behavior of that cancer cell, as well as its responsiveness to treatment.

Knowledge of molecular alterations also assists in the identification of new targets and approaches for more effective interventions. Understanding the profile of molecular changes in a cancer makes it possible to correlate the resulting phenotype of that cancer with molecular events and use those correlations to develop more effective strategies of detection, diagnosis, treatment, and prevention.

Realizing this goal will require the National Cancer Institute (NCI) to develop and apply new technologies that enable the identification of molecular changes that distinguish cancers from normal cells. New technologies will be needed to analyze the genes and gene products in isolated samples in vitro, in living cells, and in whole animals and the living body.

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- detect alterations and instabilities of genomic DNA

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